A Guide to Defective Medicinal Products

A Guide for Patients, Healthcare Professionals, Manufacturers and Distributors for reporting, investigating and recalling suspected Defective Medicinal Products.

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Contents

Introduction (1)

This guideline concerns medicinal products and the substances used in their manufacture or packaging, which are, or which may be, defective. It applies to all medicinal products and so covers licensed and unlicensed products (including specials and imported unlicensed medicinal products).

This guideline does not cover:

- Errors or “near-miss” incidents in the use or administration of medicinal products
- Suspected adverse drug reactions
- Quality defects in, or incidents involving, medical devices
- Quality defects in, or incidents involving, veterinary medicinal products.

Experience shows that it can be difficult to differentiate between defects, errors and suspected adverse drug reactions. Please see Section 3 for further information on the difference. Definitions of these and other terms used in this guideline are provided in Appendix 1. Useful contacts are provided in Appendix 3.

Because of these complexities, the initial assessment of a suspected defective medicinal product should be by a suitably qualified and experienced healthcare professional. Following the procedures outlined in this guide, the healthcare professional should decide on the appropriate classification of the "incident" and make a referral through the relevant mechanism to the appropriate organisation. This process is outlined in Section 3.

Sections 4, 5, 7 and 9 provide guidance to the pharmaceutical industry on handling and investigating suspected quality defects. In particular, it gives details of both the legal requirements and the MHRA expectations with regard to product quality related complaints, investigations and recalls. It applies to all licensed manufacturers and wholesalers, including those handling unlicensed products, and to marketing authorisation holders.

Section 8 provides guidance to healthcare professionals with regard to handling product recalls. It outlines best practice and gives guidance on when and how to inform patients of product recalls.

Throughout this guide the term “Licence Holder” has been used generically and will refer depending upon the particular circumstances to the holder of either:

- A marketing authorisation (product licence) holder, or
- A manufacturer’s Licence Holder or
- A wholesale dealer’s Licence Holder.

This guide is intended to develop over time and new editions will be published electronically when required. If you have any questions or comments about this guide, or any suggestions for improvements, please contact the Defective Medicines Report Centre directly (contact details in Appendix 2).

The Defective Medicines Centre (2)

The Defective Medicines Report Centre (DMRC) is part of the Medicines and Healthcare products Regulatory Agency (MHRA).

The role of the DMRC is to minimise the hazard to patients arising from the distribution of defective medicines by providing an emergency assessment and communication system between manufacturers, distributors, wholesalers, pharmacies, regulatory authorities and users.

It achieves this aim by:

- Receiving and assessing reports of suspected defective medicinal products for human use
- Advising and monitoring necessary actions by the responsible Licence Holder
- Communicating the details of this action to relevant parties as necessary.

The DMRC is staffed by pharmaceutical assessors and supported by administrative staff. Experts in specialist areas can be consulted when needed, for example experts in biological products, medical risk assessments or specific manufacturing techniques such as freeze-drying.

The DMRC operates a telephone line (020 3080 6574) from 08:45 to 16:45, Monday to Friday, except for public holidays, and can also be contacted directly via email at DMRC@mhra.gov.uk. Outside normal working hours, in an emergency, a MHRA Duty Officer (DO) can be contacted (Appendix 2). If needed the DO will contact the relevant professional (pharmaceutical or medical) for further advice.

Where a medicinal product recall is required, the decision is taken in consultation with the relevant Licence Holder. It is the Licence Holder's responsibility to ensure that a recall is carried out effectively throughout the distribution chain to the appropriate level. If necessary, the DMRC will issue a Recall Notification (Appendix 4) to support action taken by the Licence Holder. Further details are given in Section 5.

Medicines Recall Notifications are issued by the DMRC to a number of contacts for onward cascade to healthcare providers and professionals in the NHS and Independent sectors.

Medicines Recall Notifications are also copied to various professional and trade organisations and journals. Medicines Recall Notifications are published on the MHRA website usually within 1 working day of issue. A cumulative list of Licence Holder led recalls of UK licensed products and Medicines Recall Notifications is maintained on the MHRA website, https://www.gov.uk/drug-device-alerts.

From 1 January 2025, the MHRA regulates medicines through UK-wide marketing authorisations (MAs). For further details please see UK-wide licensing for human medicines - GOV.UK. When a potential quality defect impacts 'grandfathered' centrally authorised product (CAP) marketing authorisations (MAs) or products licensed via the International Recognition Procedure (IRP), the Licence Holder should also inform the European Medicines Agency (EMA) and the relevant National Competent Authority (NCA).

Guidance to Members of the Public and Patients (3)

This section of the guide sets out what should be done before a report is made by members of the public and patients. Members of the public and patients may also contact the MHRA or Licence Holder to seek further advice.

The section is aimed at members of the public and patients who may experience symptoms or side effects which may possibly be associated with a defective medicinal product that has been used, or that a defective product might be the explanation of these symptoms, or who may suspect that a medicinal product may be defective prior to use.

The purpose of the process is:

- To distinguish events caused by defective products from those experienced due to listed side effects or accidents
- To differentiate between events relating to medicines from those relating to medical devices
- To ensure that before any report is made to the MHRA, all necessary information has been assembled in order to aid investigation.

It is important that patients do not stop their treatment. If a medicine is suspected to be defective, patients should consult their pharmacist or GP if they have concerns about continuing their treatment.

The suspected defective products should be retained and preserved as they may be required for analysis.

During the manufacture or distribution of a medicine, an error or incident may occur whereby the finished product does not conform to its specification or is for some other reason defective (e.g. presence of a contaminant which may not be detected during routine analysis). While such a defect may impair the effect of the product and present undesirable side effects, it should not be confused with a suspected Adverse Drug Reaction where the product conforms to its specification, but undesirable side effects are observed. Advice from a Pharmacist or GP can help to differentiate between suspected adverse drug reactions and defective medicinal products. Further details on reporting suspected adverse drug reactions can be found in Appendix 3.

Lack of efficacy and changes in side effects can be experienced with switches from branded to generic products or from branded to parallel imported products, patients should consult their pharmacist, or GP should they have any concerns.

If the suspected defect is associated with an undesirable side effect or suspected adverse drug reaction that may have occurred due to a quality defect, there are some additional questions which should be asked:

- Was the product stored correctly? (To exclude incorrect storage as the cause of the suspected defect)
- Has the product been used as instructed by your GP or Pharmacist? (to exclude issues with administration techniques, for example for inhalers or applying medicated skin patches)
- If the defect is visible, was the defect identified in a new previously unopened container or had the container previously been used? (To exclude user errors such as product mix-ups)
- Are there other unopened containers of the same batch available, which could be checked?
- If the product is used with a medical device, could the device be the cause of the incident?

Reports on suspected defective medicinal products should include the nature of the defect and the following information from the packaging of the medicines:

- The product brand or the non-proprietary(generic) name
- The name of the manufacturer, supplier or parallel importer
- The strength and dosage form of the product
- The product licence (PL) number
- The batch number
- The expiry date or dates of the product.

An electronic reporting form for healthcare professionals and patients to report potentially defective medicines can be accessed via the MHRA Yellow Card Reporting Portal, http://www.mhra.gov.uk/yellowcard).

Alternatively, a verbal or email report can be made directly to DMRC using the contact details in this document. The DMRC may ask you to provide samples directly to the manufacturer for analysis and we will ask the company to investigate the suspected defect. The company are best placed to review the records of manufacture and packaging and have the analytical methods and equipment in place to test the complaint sample and retained samples. The DMRC will critically review the company's investigation and testing results. If the investigation or testing is not satisfactory, then independent testing may be performed by the MHRA Laboratories. In addition, the company's investigation and testing of suspected defects are reviewed by the MHRA Inspectorate as part of the routine Good Manufacturing Practice (GMP) inspections. As the investigation may require clarification about how the product was stored or used, it is helpful for the reporter to provide consent to be contacted. This allows the company to gather any additional context that may be important to the assessment.

Once you have reported a suspected defective medicinal product to the DMRC, the DMRC will carry out an assessment and, if necessary, an investigation. You should be informed of any significant developments and will always receive a concluding communication outlining the results and conclusions of the DMRC's investigations. Depending on the nature of the suspected defect and product, and the complexity of any further testing or investigation, it may take several weeks before any conclusions can be drawn. If you do have any concerns regarding the progress of an investigation you should ask for a progress report.

Initial Assessment of Suspected Defective Medicinal Products by Healthcare Professionals (4)

This section of the guide sets out what should be done by healthcare professionals before any contact is made with the MHRA or the Licence Holder. Healthcare professionals may also contact the MHRA or Licence Holders to seek further advice. This guidance can also be followed by others who may receive reports of suspected defective medicinal products such as wholesale dealer Licence Holders, trading standards departments, etc. This guidance does not replace local procedures.

In some circumstances, healthcare professionals may feel that they do not have the necessary skills or experience to determine whether a medicinal product is defective. Advice may be available via the local NHS Hospital Quality Control/Assurance Pharmacist, Medicines Information Unit, the DMRC or the Licence Holder or manufacturer.

This section is aimed at healthcare professionals who may observe clinical symptoms or a patient event, which indicates that a defective medicinal product has been used, or that a defective product might be the explanation of this observation, or who may recognise that a medicinal product may be defective prior to use.

The purpose of the process is:

- To distinguish events caused by defective products from those due to suspected adverse drug reactions, accidents or errors
- To differentiate between events relating to medicinal products from those relating to non-medicinal plant, and equipment, and medical and non-medical supplies
- To ensure that before any report is made to the MHRA, all necessary information has been assembled. When reporting a serious defect, it is more important to report it to the MHRA as soon as possible and obtain the full information at a later stage
- To provide reporting officers with the means to assess the seriousness of what is to be reported, before contact is made with the MHRA
- To provide information to the MHRA that would indicate whether or not national action may be required.

The procedure described does not affect the responsibility of staff to take any necessary local action arising from any incident either before or after notification to the Agency, which may be:

- To prevent the use of a defective or possibly defective medicinal product
- To preserve evidence for future need as enquiries progress. Material evidence must be preserved and put in the charge of a responsible person/officer
- To prevent interference with equipment used with a defective or possibly defective medicinal product, except for safety reasons or to prevent loss of samples and where appropriate to witness and record dial readings, position of taps and switches, etc.
- To report the incident to the Learn from patient safety events (LFPSE) service and/or local error or incident reporting scheme where such a scheme exists.

The suspected defective medicinal product must be retained and preserved. If samples are required for analysis or other purposes, they should ideally be obtained from another part of the same batch. If these samples would not provide the information needed the material implicated should be used. It should be noted that where a defect is limited to a single unit or a limited number of units, analysis of a random sample might give misleading results.

On occasion, Coroners may wish to impound defective or possibly defective medicinal products. The Department of Health and Social Care has an agreement with the Coroners Society for such materials to be released if this is necessary to allow the investigation to proceed.

Where the health of a patient has been adversely affected either because of a suspected adverse drug reaction, or lack of efficacy, as much information regarding a clinical incident should be obtained as possible, to allow assessment of the incident.

During the manufacture or distribution of a medicine, an error or incident may occur whereby the finished product does not conform to its specification or is for some other reason defective (e.g. presence of a contaminant which may not be detected during routine analysis). While such a defect may impair the therapeutic effect of the medicinal product and could adversely affect the health of the patient, it should not be confused with a suspected adverse drug reaction where the medicinal product conforms to its specification, but a suspected adverse incident is observed. Advice from suitably trained and experienced healthcare professionals, from the MHRA or from the Licence Holder, can help to differentiate between suspected adverse drug reactions and defective medicinal products. Further details on reporting suspected adverse drug reactions can be found in Appendix 3.

An increase in the incidence of a suspected adverse drug reaction(s), which appears to be associated with one batch of a product, does not necessarily indicate that there is a quality defect with a medicinal product. Similarly reports of lack of efficacy may not indicate that

there is a quality defect. Lack of efficacy and changes in suspected adverse drug reaction reporting rates are commonly reported with switches from branded to generic products or from branded to parallel imported products. While these types of incidents are rarely caused by quality defects, they should always be investigated initially as suspected defective products.

If the medicinal product concerned is confirmed for human use, and if the suspected defect is associated with a suspected adverse drug reaction that may have occurred due to a quality defect, there are some additional questions which should be asked:

- Was the medicinal product stored correctly? (To exclude incorrect storage as the cause of the suspected defect)
- If the defect is visible, was the defect identified in a new previously unopened container or had the container previously been used? (To exclude user errors such as product mix-ups)
- Are there other unopened containers of the same batch available, which could be checked?
- If the product requires preparation, such as addition of a diluent, was the correct procedure followed and/or correct diluent used?
- If the medicinal product is used with a medical device, could the device be the cause of the incident?

The Defective Medicines Report Centre (DMRC) operates a 24-hour service to assist with the investigation of problems arising from medicinal products thought to be defective and to co-ordinate any necessary protective action. The DMRC team are available via a telephone line (020 3080 6574) from 08:45 to 16:45, Monday to Friday, except for public holidays, and can also be contacted directly via email at DMRC@mhra.gov.uk. Outside normal working hours, in an emergency, a MHRA Duty Officer (DO) can be contacted (Appendix 2). If needed the DO will contact the relevant professional (pharmaceutical or medical) for further advice.

Because of the nature of medicinal products, careful assessment of a case needs to be made to ascertain whether it is to be reported.

Reports on suspected defective medicinal products should include:

- The brand or the non-proprietary (generic) name
- The name of the manufacturer, supplier or parallel importer
- The strength and dosage form of the product
- The product licence (PL) number
- The batch number or numbers of the product
- The expiry date or dates of the product
- The nature of the defect
- The account of any action taken in consequence.

An electronic reporting form for healthcare professionals and patients to report potentially defective medicines can be accessed via the MHRA Yellow Card Reporting Portal, http://www.mhra.gov.uk/yellowcard).

Licence holders, or nominated representatives, should report defectives directly via the online reporting form, accessed via https://icsrsubmissions.mhra.gov.uk/login. For more information see Appendix 7.

Alternatively, a verbal report can be made, and should always be made, if the report concerns a critical or major defect, or is outside of office hours. A flowchart for the assessment of suspected quality defects in medicinal products can be found in Appendix 6.

The DMRC may ask you to provide samples directly to the manufacturer for analysis; and we will ask the company to investigate the suspected defect. The company are best placed to review the records of manufacture and packaging and have the analytical methods and equipment in place to test the complaint sample and retained samples. The DMRC will critically review the company's investigation and testing results. If the investigation or testing is not satisfactory, then independent testing may be performed by the MHRA Laboratories. In addition, the company's investigation and testing of suspected defects are reviewed by the MHRA Inspectorate as part of the routine Good Manufacturing Practice (GMP) inspections. As the investigation may require clarification about how the product was stored or used, it is helpful for the reporter to provide consent to be contacted. This allows the company to gather any additional context that may be important to the assessment.

Once you have reported a suspected defective medicinal product to the DMRC, the DMRC will carry out a further assessment and, if necessary, an investigation. You should be informed of any significant developments and will always receive a concluding communication outlining the results and conclusions of the DMRC's investigations. Depending on the nature of the suspected defect and product, and the complexity of any further testing or investigation, it may take several weeks before any conclusions can be drawn. If you do have any concerns regarding the progress of an investigation you should ask for a progress report.

Investigation of Suspected Defective Medicinal Products – The Licence Holder and the DMRC (5)

To accord with the requirements of the Human Medicines Regulations 2012 [SI 2012/1916] the holder of a manufacturer's licence must comply with the principles and guidelines for good manufacturing practice set out in the Good Manufacturing Practice Directive 2003/94/EC. *(Regulations 37 to 41 of the Human Medicines Regulation 2012 [SI 2012/1916]).*

Directive 2003/94/EC requires that the manufacturer shall implement a system for recording and reviewing complaints together with an effective system for recalling, promptly and at any time, medicinal products in the distribution network. Any complaint concerning a defect shall be recorded and investigated by the manufacturer. The manufacturer shall inform the competent authority of any defect that could result in a recall or abnormal restriction on supply and, in so far as is possible, indicate the countries of destination. Any recall shall be made in accordance with the requirements referred to in Part 5 of the Human Medicines Regulations 2012*(Directive 2003/94/EC Article 13(2)).* This is supported by Chapter 8 of the EU Good Manufacturing Practice Guidelines.

These conditions place a statutory duty on the holder of a manufacturer's licence to inform the licensing authority immediately when they become aware of any defect which could result in a recall.

In distributing a medicinal product by way of wholesale dealing, the manufacturer's Licence Holder must comply with the guidelines on good distribution practice in the case of a Licence Holder in Great Britain, published under, or that apply by virtue of regulation C17, or in the case of a Licence Holder in Northern Ireland, published by the European Commission in accordance with Article 84 of the 2001 Directive, as if the Licence Holder were the holder of a wholesale dealer's licence *(Regulation 39(8) of the Human Medicines Regulation 2012 [SI 2012/1916]).* These guidelines also support the process of medicinal product recalls.

Where a medicinal product is to be manufactured in a country other than the United Kingdom the applicant for the marketing authorisation relating to that product should get an undertaking from the non-United Kingdom manufacturer that the non-United Kingdom manufacturer has implemented a system for recording and reviewing complaints in relation to medicinal products to which the marketing authorisation relates, together with an effective system for recalling promptly and at any time the medicinal products in the distribution network. The non-United Kingdom manufacturer must record and investigate all these complaints and must immediately inform the licensing authority of any defect which could result in a recall from sale, supply or export or in an abnormal restriction on such sale, supply

or export. *Regulation 50((4) and Schedule 9 of the Human Medicines Regulation 2012 [SI 2012/1916]).*

Manufacturers who notify the Licensing Authority when a recall has already commenced will breach the regulations. It is not always clear whether a recall will be necessary; in these circumstances manufacturers should always contact the DMRC for advice.

Reports or complaints regarding defective medicinal products may be reported to the manufacturer by the originator of the report directly or via the DMRC; alternatively potential defects may be identified through routine product quality surveillance by the manufacturer or by the Medicines Testing Scheme of the MHRA.

Occasionally reporters to the DMRC will ask to remain anonymous; the DMRC must respect this, although it may make some investigations more difficult to conclude. The MHRA privacy notice (https://www.gov.uk/government/publications/mhra-privacy-notice/mhra-privacy-notice) describes how we collect and use your personal information, in accordance with the Data Protection Act 2018 and the General Data Protection Regulation (GDPR) 2016/279.

Where the manufacturer is reporting a defect to the MHRA, the Licence Holder should use the online Defect Reporting Form, Appendix 7. If an urgent notification to the DMRC is required or where a notification is required outside normal working hours, at weekends or on Public Holidays, a telephone call should be prioritised, in lieu of completing the online Defect Reporting Form:

- **During office hours (8:45am to 4:45pm Monday to Friday)**
    - Telephone: 020 3080 6574 (DMRC Only) / E-mail: dmrc@mhra.gov.uk
- **Outside normal working hours, at weekends or on Public Holidays, for emergencies only:**
    - Telephone: 07795 641 532

The DMRC will initially require the following information as a minimum:

- Dates of manufacture and release of the affected product batch(es) to the market.
- An impact assessment quantifying the number of batches affected, and suitable proposals for market action (recall, quarantine or other mitigating containment actions), if these are to be considered.

- Where admixture has occurred, dates of manufacture and release of the admixed product, closest to the complaint batch.
- Batch sizes and pack size.
- Date of first and last distribution to the market.
- Review of complaint records for reports of similar defects.
- Estimation of stock under the Licence Holder's control.
- Has the same batch been distributed to other countries?

Depending on the nature of the reported defect, the Licence Holder may also be required to quarantine any remaining stock while an investigation is carried out. In potentially serious cases, this quarantine may be extended to the wholesale distribution chain.

The following may also be required if further investigation is needed after the initial review:

- Licence holder risk assessment, including, if appropriate, a clinical assessment
- A review of all associated batch manufacturing, packaging, testing, release and distribution records for anomalies which may explain the suspected defect
- Examination, and retesting, if appropriate, of retained samples
- Details of any actions to be taken by the Licence Holder to correct the defect in the future.
- Timescales vary considerably depending on the nature of the defect, the consequent risk to public health, and the likely complexity of the investigation.

Where the DMRC has concerns, specific deadlines may be imposed. Where Licence Holder's encounter problems meeting these deadlines, they should discuss these with the DMRC.

Information relating to the reported defect is fed into the Risk-based inspection (RBI) process. The Inspector may wish to examine the Licence Holder's records of a defect investigation at an inspection.

Recalling Defective Medicinal Products – The Licence Holder and the DMRC (6)

In almost all cases the decision to recall a product or batch is made following consultation between the DMRC and the Licence Holder. Although the MHRA has regulatory powers to require a recall, these are rarely used, provided that Licence Holder's work openly and closely with the MHRA.

Once a decision to recall a batch or batches of product(s) has been taken, a number of further decisions need to be taken:

i) What is the level of risk?

The MHRA uses an internationally agreed classification system for medicines recalls:

Medicines Recall/Notification Classification	Defect risk classification
National Patient Safety Alert (NatPSA) equivalent to Class 1 Medicines Recall	The defect presents a risk of death or disability. These alerts will be issued via the Central Alerting System (CAS) as National Patient Safety Alerts. Please note that all Class 1 Medicines Recalls, will be issued as National Patient Safety Alerts and will be provided in the specific format, see Appendix 5 (https://www.england.nhs.uk/patient-safety/national-patient-safety-alerting-committee/). The details relating to the recall will be accessible via the normal routes on the MHRA website, (https://www.gov.uk/drug-device-alerts) and linked directly via the National Patient Safety Alert.
Class 2 Medicines Recall	The defect may cause mistreatment or harm to the patient, but it is not life-threatening or serious. Note that a NatPSA may be issued for any type of defect that presents a risk of death or disability.

Class 3 Medicines Recall	The defect is unlikely to cause harm to the patient, and the recall is carried out for other reasons, such as non-compliance with the marketing authorisation or specification. Note that a NatPSA may be issued for any type of defect that presents a risk of death or disability.
Class 4 Medicines Notification	The MHRA also issues “Caution in Use” notices, where there is no threat to patients or no serious defect likely to impair product use or efficacy. These are generally used for minor defects in packaging or other printed materials. “Caution in Use” notices may also be issued where a defect has been identified but due to supply concerns product cannot be recalled, in these instances the alert will be used to provide advice to healthcare professionals. Note that a NatPSA may be issued for any type of defect that presents a risk of death or disability.
Company-led Medicines Recall/Notification	These are issued where the Licence Holder is able to identify the affected customers, therefore it is not necessary to issue an alert to the entire NHS/healthcare system, as the issue is only relevant to a small number of recipients.

National Patient Safety Alerts

The Medicines and Healthcare products Regulatory Agency (MHRA) is now an accredited issuer of National Patient Safety Alerts. All safety-critical alerts for medicines and medical devices that require a system wide response will be issued as National Patient Safety Alerts.

These alerts follow the criteria and template agreed by the National Patient Safety Alerting Committee (NaPSAC).

All Class 1 Medicines Recalls will meet the National Patient Safety Alert criteria and will be issued as National Patient Safety Alerts (NatPSA). These will be issued from and published on the CAS website and will also be published on the MHRA website. Responses will be collected via the CAS website from NHS Trusts and Foundation Trusts. Recalls and Notifications that do not meet the National Patient Safety Alert criteria will not be published on the CAS website.

Further information on the role and scope of National Patient Safety Alerts can be found on the following link: https://www.england.nhs.uk/patient-safety/national-patient-safety-alerting-committee/

The issue of a NatPSA does not change the procedure and requirements for Licence Holder's when issuing alerts. NatPSA will be clearly marked to identify the internationally agreed classification system for medicines recalls and the timelines for actions will be aligned with this classification.

ii) Should the recall be to Distributor, Pharmacy/GP Surgery/Shop (in the case of GSL products) or patient level?

This depends on the nature of the risk, the amount of time that has elapsed since the batch was first distributed and the type of product.

In most cases, a National Patient Safety Alert (equivalent to a Class 1 recall) should be to patient level; however, this may not be the appropriate action if alternative medicine is not available, an assessment of the overall risk to patients must be conducted. Also, consideration has to be given to the difficulties of communicating recall information to patients. Licence holders may need to arrange press releases and advertising campaigns.

Most recalls are of Class 2 or 3. Patient level recalls are rarely required for this level of risk, and recalls may present a greater risk to the patient than continuing treatment. Occasionally Class 2 or 3 recalls can be carried out just to wholesaler level in circumstances where stock is unlikely to be found further down the supply chain and the level of risk is sufficiently low.

iii) Should the Licence Holder's recall action be supported by a MHRA Medicines Recall Notification?

This will depend on the amount of product distributed, the likely number of customers, and the nature of the risk. For example, if the Licence Holder has distributed relatively small volumes to a few customers and is able to contact these customers directly, a MHRA

Medicines Recall Notification is unlikely to contribute significantly to the effectiveness of the recall and may be more disruptive.

Where distribution is widespread and/or the risk is serious, then a MHRA Medicines Recall Notification provides a mechanism to achieve blanket coverage to as many healthcare professionals as possible.

Even when a MHRA Medicines Recall Notification is issued, the recall is still the responsibility of the Licence Holder, as indicated at the beginning of the previous section. Action taken by the MHRA is secondary to, and supportive of the action taken by the Licence Holder. The Agency will work with the Licence Holder where a Medicines Recall/Notification is required.

In the event of a recall the Licence Holder should consider a strategy for returns and refunds; this should be devised in consultation with the Department of Health and Social Care, where applicable. MHRA do not get involved in any financial aspects of product recall.

iv) Guidance on letter drafting for marketing authorisation holders

In some instances, the MHRA may request that a direct healthcare professional communication (DHPC) is shared alongside a medicines recall/notification. Further guidance is available here.

A DHPC aims to ensure safe and effective use of a marketed medicine. Letters are sent directly to healthcare professionals by marketing authorisation holders or by the licensing authority. Direct healthcare professional communications should not include any material that might constitute advertising or be considered promotional or commercial.

Guidance for marketing authorisation holders

- EU good pharmacovigilance practice (GVP) Module XV (Safety communication) provides guidance to marketing authorisation holders on how to communicate and coordinate safety information concerning medicinal products authorised in the UK, including via direct healthcare professional communications. In addition, GVP Annex II includes templates for direct healthcare professional communications and communication plans, which should be used for UK authorised products. UK-specific requirements in relation to the dissemination of DHPCs are outlined in a UK statutory guidance note.

- Irrespective of the licensing route for a UK authorised product, marketing authorisation holders should submit both the draft and finalised versions of DHPCs and communication plans to the MHRA

via pharmacovigilanceservice@mhra.gov.uk and should wait until comments are received before disseminating in the UK.

Call for reporting

- All UK direct healthcare professional communication letters should always include a 'Call for reporting' section to outline national arrangements for reporting suspected adverse drug reactions.

- The Template 'Call for Reporting' sections for UK letters should be used to encourage reporting to the Yellow Card scheme. Additional text should be considered for medicines subject to additional monitoring and for biological/biosimilar medicines and vaccines.

Recalling Defective Medicinal Products – The Responsibilities of Distributors (7)

To accord with the requirements of the Human Medicines Regulations 2012 [SI 2012/1916] the holder of a wholesale dealers licence must comply with the guidelines on good distribution practice. In the case of a Licence Holder in Great Britain, these guidelines would be published under, or that apply by virtue of regulation C17, or in the case of a Licence Holder in Northern Ireland, published by the European Commission in accordance with Article 84 of the 2001 Directive. The holder must maintain an emergency plan to ensure effective implementation of the recall from the market of a medicinal product where recall is either ordered by the licensing authority (or by the competent authority of any EEA State in the case of Northern Ireland), or carried out in co-operation with the manufacturer of, or the holder of the marketing authorisation of the product (see section 4). The holder must also keep documents relating to the sale or supply of medicinal products under the licence which may facilitate the withdrawal or recall from sale of medicinal products in accordance with their emergency plan. (Regulation43(7) of the Human Medicines Regulations 2012 [SI 2012/1916]).

The holder of the wholesale dealer's licence should have in place detailed procedures that describe the action to be taken when a recall notice is received and must take appropriate steps to inform all customers who may have received stock of the batch(es) and medicinal product(s) which are affected by a recall.

Wholesalers should be aware that not all recalls will be accompanied by a Medicines Recall Notification issued by the MHRA and may be instituted at the request of a manufacturer or Licence Holder. In all cases the MHRA should have been notified of a recall in advance (see section 5).

If a wholesaler has any doubts about a recall, they should contact the DMRC for advice.

Where a wholesaler receives a complaint regarding a suspected defective medicinal product, it should be referred to the relevant Licence Holder, manufacturer and/or the DMRC.

Note: Manufacturers Licence Holders are by their nature carrying out wholesale distribution activities and should note the specific requirements set out in this guidance document.

Recalls – Healthcare Professionals' Responsibilities (8)

MHRA National Patient Safety Alerts, Medicines Recalls and Notifications are published on a dedicated section of our website. The publishing of a National Patient Safety Alert, Medicine Recall or Notification automatically triggers an email notification to anyone who has registered to receive such notifications. Any individual can sign up via our e-mail alerting service.

Separate arrangements exist for the cascade of Medicines Recall Notifications in Northern Ireland, Scotland and Wales. Details of where the respective information is published can be found below:

- Northern Ireland: https://www.health-ni.gov.uk/topics/pharmacy
- Scotland: https://www.sehd.scot.nhs.uk/index.asp
- Wales: https://www2.nphs.wales.nhs.uk/contacts.nsf

Licence holder led recalls are usually addressed directly to recipients of the affected batch(es), or via notices on delivery notes from wholesale dealers. Whichever form the recall takes, the principles of this section apply.

The Medicines and Healthcare products Regulatory Agency (MHRA) is now an accredited issuer of National Patient Safety Alerts. All safety-critical alerts for medicines and medical devices that require a systemwide response will be issued as National Patient Safety Alerts. These alerts follow the criteria and template agreed by the National Patient Safety Alerting Committee (NaPSAC). The information will continue to be cascaded to the Devolved Administrations as per the MHRAs national remit.

Any National Patient Safety Alert or Medicines Recall Notification will contain an outline of what actions must be taken; in some cases, this may also be followed up with further details from the Licence Holder in a subsequent communication. Recipients of recall notices should have in place local procedures that identify the actions that need to be taken in response to each recall notice, whether a DMRC Medicines Recall Notification or a Licence Holder recall.

There is guidance about the arrangements which should be in place for the handling of any National Patient Safety Alerts.CAS Liaison Officers should agree an escalation route to ensure Executive oversight for the implementation of actions required in these Alerts and Executive authorisation for recording 'action complete' on CAS, as we know that some Liaison Officers do not currently have a role in the response to MHRA Medicines

Recalls/Notifications. This escalation route would need to encompass National Patient Safety Alerts related to defective medicines designated as ‘straightforward’ and National Patient Safety Alerts related to defective medicines designated as ‘complex’. ‘Complex’ designation would typically apply if there is a need to identify and intervene with patients who have already received the medication, rather than solely remove stock before it can be used.

In the unlikely event, local procedures should include actions to take should a recall notification be received towards the end of the afternoon or out of hours.

Regional Pharmaceutical Officers and local teams should ensure a designated position/person is responsible for receiving and disseminating DMRC Medicines Recall Notifications to the appropriate level. These actions and roles will be subject to review by the Care Quality Commission and the General Pharmaceutical Council.

Instructions within Medicines Recall Notifications need to be acted upon appropriately, examples of each class of Medicines Recall Notification are given in Appendix 4, the actions which should be taken are as follows:

<u>Healthcare Professionals responsible for cascading recall information</u>

1. Read the Medicines Recall Notification/NatPSA and identify who it is intended for

    - If it is a specialist product, it may only need to be cascaded to limited numbers of recipients

2. Identify the Class of the Medicines Recall Notification

    - The MHRA avoids issuing any notifications, apart from those which are potentially serious or life threatening (i.e. NatPSA/Class 1) on Fridays, especially prior to public holidays

    - The timescales specified on Medicines Recall Notifications are for advice to give some indication of the priority with which action must be taken

    - Additional consideration should be given to the mechanism of cascade and the likely time for it be received and acted on by the relevant healthcare professional

    - A local assessment of the most appropriate mechanism and timing for the cascade should be taken by the relevant healthcare professional(s).

Healthcare Professionals supplying medicines e.g. pharmacies, hospitals (NHS or Private), dispensing doctors, etc.

1. Check if you have had any stock of the affected product using the information provided in the Medicines Recall Notification

    - Each Medicines Recall Notification gives distribution dates as well as batch and expiry information. If, based on the information provided, it is unlikely that you have had any of the affected products, you do not need to do anything else, e.g. if you have not had any deliveries since the date of first distribution of the product, you are unlikely to have any stock

2. If you have stock of the affected product, place this in quarantine

    - Consider outstanding orders and recent deliveries, these may have been dispatched before the recall notice was issued

3. If you have supplied products for stock to other organisations ensure that they are aware of the recall, e.g. community pharmacists providing services to care homes or hospital pharmacies providing services to ambulance trusts

4. For patient level recalls check dispensing records, and identify patients who have received the affected batches

    - If you are not able to identify batch numbers or suppliers from your records you may need to contact every patient who has received the named product since the date of first distribution

    - If a patient level recall is needed, the Licence Holder may also consider public announcements

    - Healthcare professionals involved in prescribing may need to be prepared to provide replacement stock for the patient, and may need to make arrangements for new prescriptions; in certain circumstances you may need to consider making an emergency supply (see the current edition of Medicines Ethics and Practice published by the Royal Pharmaceutical Society, RPS, for further information)

5. If you have problems or queries regarding the recall you should contact the Licence Holder via the contact details given on the Medicines Recall Notification

6. If you have problems with the quality of the text, or other transmission issues, you should contact the next level of the cascade up from you. You should ensure that you

know who this is, e.g. for community pharmacists and GPs this will usually be the local teams

7. If neither of the above is able to help, you should contact the DMRC

8. Advice within Medicines Recall Notifications should not override professional judgment in making decisions in the best interest of their patient.

General Practitioners and Dental Surgeons do not normally have to do anything on receipt of a recall notice, unless it is for a product that is used in their practice, in their box/bag used for home visits or when on-call, and where the recall is to patient level. Recall information is provided for information, and particularly in case of any unexpected reactions experienced by their patients, which might have been caused by the suspected quality defect. The communication process should ensure that all doctors and other healthcare professionals in their practices are made aware of any recall notices where appropriate.

Healthcare professionals involved in cascading or responding to medicines recalls should ensure that they fully document any action that they take with regards to a recall.

Follow-Up – The Licence Holder and the DMRC (9)

The Licence Holder should draw their own conclusions regarding a suspected defect and present them to the DMRC with the relevant supporting data. Where the Licence Holder is not sure about their conclusions they should contact the DMRC for advice. The professional staff of the DMRC will then assess, referring to other experts within the MHRA if needed, and advise the Licence Holder if they support their decision, if further questions need to be answered or if alternative or additional action is needed.

Whenever a formal investigation is carried out, the investigation is only closed when the DMRC issues a closing response. If you are not sure if an investigation is completed, you should request an update on the current status from the DMRC. Where a recall is required, a closing response will not be issued until a final report on the recall is received.

The Licence Holder should provide regular updates on the progress of an investigation into the cause and conduct of a recall. In the longer term, over a period that should be agreed with the DMRC, a final report should be provided no later than 12 weeks after the initial report unless otherwise agreed. Where Licence Holder's encounter problems meeting these deadlines, they should discuss with the DMRC directly.

Whichever mechanism is used, the Licence Holder will need to provide the DMRC with regular updates regarding the progress of the recall. These reports should include a summary reconciliation between the amount of product supplied to the market and the amount returned up to the date of the report. It is not possible to specify a percentage which should be expected to be returned because this will vary depending on the particular circumstances of a recall. After a period, agreed with the DMRC, a final report will be required to close the recall.

Appendix 1 – Glossary and Acronyms

Glossary

ACCIDENT	An event that could not have been reasonably foreseen.
ADVERSE DRUG REACTION	Any untoward and unintended response in a subject to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product
DEFECT/DEFECTIVE	Not conforming to specification. * A shortcoming.
DEFECTIVE MEDICINAL PRODUCT	Proves to be harmful under normal conditions of use. Lacking in therapeutic efficacy. The qualitative and quantitative composition of the product is not as declared. The controls on the medicinal product and/or on the ingredients and the controls at an intermediate stage of the manufacturing process have not been carried out or if some other requirement or obligation relating to the grant of the manufacturing authorisation has not been fulfilled.
HAZARDOUS/CRITICAL DEFECT	A defect, which has the capability to adversely affect the health of the patient. *
MAJOR DEFECT	A defect which impairs the therapeutic activity of the product. It may not be hazardous. *
MINOR DEFECT	A defect, which has no important effect upon the therapeutic activity of the product and does not otherwise produce a hazard.
ERROR	A wrong action by a person.

INCIDENT	A definite and separate occurrence; an event that interrupts normal procedure
LACK OF EFFICACY	The medicinal product does not produce the desired or expected effect
LICENCE HOLDER	Refers to the relevant marketing authorisation (product licence) holder, manufacturers Licence Holder or wholesale dealer Licence Holder as appropriate.
MEDICAL DEVICE	Any instrument, apparatus, appliance, material or other article, whether used alone or in combination, together with any software necessary for its proper application intended by the manufacturer to be used on human beings for the purpose of: diagnosis, prevention, monitoring, treatment or alleviation of disease, diagnosis, monitoring, treatment, or alleviation of or compensation for an injury or handicap, investigation, replacement or modification of the anatomy or of a physiological process, control of conception and which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, even if it is assisted in its function by such means".
MEDICINAL PRODUCT	Any substance or combination of substances presented as having properties for treating or preventing disease in human beings Any substance or combination of substances which may be used in or administered to human beings with a view to making a medical diagnosis or to restoring, correcting or modifying physiological functions

SPECIAL MEDICINAL PRODUCT	A product within the meaning of Regulation 167 or any equivalent legislation in an EEA State [a country] other than the United Kingdom;
NATIONAL PATIENT SAFETY ALERT (NatPSA)	An alert issued that meets the criteria as defined by the National Patient Safety Committee. The criteria for issuing an alert will ensure: alerts are only issued for safety-critical issues (risk of death or disability) alerts have a concise and clear explanation of the risk the required actions are assessed for feasibility, risk of unintended consequences, equalities impact, effectiveness, and cost-effectiveness the actions are SMART (specific, measurable, achievable, realistic and timely) The introduction of these new alerts is expected to result in a lower number of national alerts being issued. National Patient Safety Alerts have a distinct design and unique logo to make them stand out from other safety communications.

*Based upon definitions in British Standards BS 6001 “Sampling Procedures”

Acronym List

Acronym	**Full Meaning**
API	Active Pharmaceutical Ingredient
BS	British Standards
CAS	Central Alerting System
CAP	Centrally Authorised Product
CQC	Care Quality Commission
CRO	Contract Research Organisation
DMRC	Defective Medicines Report Centre
DO	Duty Officer
DHSC	Department of Health and Social Care
DHPC	Direct Healthcare Professional Communication
EEA	European Economic Area

EMA	European Medicines Agency
E2B R3	ICSR Messaging Standard (E2B Revision 3)
EU	European Union
GDPR	General Data Protection Regulation
GMP	Good Manufacturing Practice
GPhC	General Pharmaceutical Council
GSL	General Sales List
GPvP	Good Pharmacovigilance Practice
HCP	Healthcare Professional
HLGT	High Level Group Term
HLT	High Level Term
HSE	Health and Safety Executive
ICSR	Individual Case Safety Report
IRP	International Recognition Procedure
LLT	Lowest Level Term
LFPSE	Learn From Patient Safety Events
MA	Marketing Authorisation
MAH	Marketing Authorisation Holder
MEP	Medicines, Ethics and Practice
MHRA	Medicines and Healthcare products Regulatory Agency
MedDRA	Medical Dictionary for Regulatory Activities
NCA	National Competent Authority
NatPSA	National Patient Safety Alert
NaPSAC	National Patient Safety Alerting Committee
NHS	National Health Service
NI	Northern Ireland
PL	Product Licence
PT	Preferred Term
RPS	Royal Pharmaceutical Society
SI	Statutory Instrument
SOC	System Organ Class
UI	Unique Identifier
UK	United Kingdom
VMD	Veterinary Medicines Directorate
YC	Yellow Card

Appendix 2 – DMRC Contact Details

Contact address for submitting reports, samples or for advice:

The Defective Medicines Report Centre, 10 South Colonnade, Canary Wharf, London, E14 4PU

During office hours (8:45am to 4:45pm Monday to Friday)

Telephone: 020 3080 6574 (DMRC Only)

E-mail: dmrc@mhra.gov.uk

Outside normal working hours, at weekends or on Public Holidays, for emergencies only:

Telephone: 07795 641 532

Website: http://mhra.gov.uk/

The website provides further information regarding the DMRC, access to previous Medicines Recall Notifications and the online reporting form.

For general enquiries to the MHRA contact:

Tel: 020 3080 6000

E-mail: info@mhra.gov.uk

Appendix 3 – Useful Contacts

To report a suspected Adverse Drug Reaction:

Report online at http://www.mhra.gov.uk/yellowcard

Yellow Card forms are available:

- by emailing yellowcard@mhra.gov.uk
- If you cannot complete the online report or form, for reporting, you can call us on 0800 731 6789 (9am to 5pm Monday to Friday).
- by writing to FREEPOST YELLOW CARD (no other address details necessary)

For other general queries about the MHRA or if you cannot complete the online form you can call the MHRA Customer Service Line on 0203 080 6000 (9am to 5pm Monday to Friday) Contact Us | Making medicines and medical devices safer

To report incidents or defects involving Medical Devices:

Adverse Incident Centre (Medical Devices), MHRA, 10 South Colonnade, Canary Wharf, London, E14 4PU

Adverse incidents involving medical devices cannot be reported by telephone. Please report online or by email to aic@mhra.gov.uk

- If following up on an existing report, please always include the Yellow Card report ID when contacting us.

Or via the MHRA website http://www.mhra.gov.uk/yellowcard

To report suspected quality defects or incidents with medicinal products for use in animals:

Veterinary Medicinal Products, Veterinary Medicines Directorate, Woodham Lane, New Haw, Weybridge, Surrey, KT15 3NB

Telephone: 01932 336 911 or via the website http://www.vmd.defra.gov.uk/

To report patient safety incidents, near misses or errors, not related to quality defects in medicinal products or suspected adverse drug reactions:

Learn from patient safety events (LFPSE) service, NHS England

Reporting via https://www.england.nhs.uk/patient-safety/patient-safety-insight/learning-from-patient-safety-events/learn-from-patient-safety-events-service/

To report specific concerns in relation to a pharmacy services, including dispensing and pharmacy professionals:

General Pharmaceutical Council, Level 14, 1 Cabot Square, London, E14 4QJ

Telephone: 020 3713 8000

Email: info@pharmacyregulation.org

Or via the website https://www.pharmacyregulation.org/about-us/contact-us

To report specific concerns in relation to a healthcare provider:

Care Quality Commission, 2 Redman Place, London, E20 1JQ

Telephone: 03000 616161

Email: enquiries@cqc.org.uk

Or via the website https://www.cqc.org.uk/contact-us

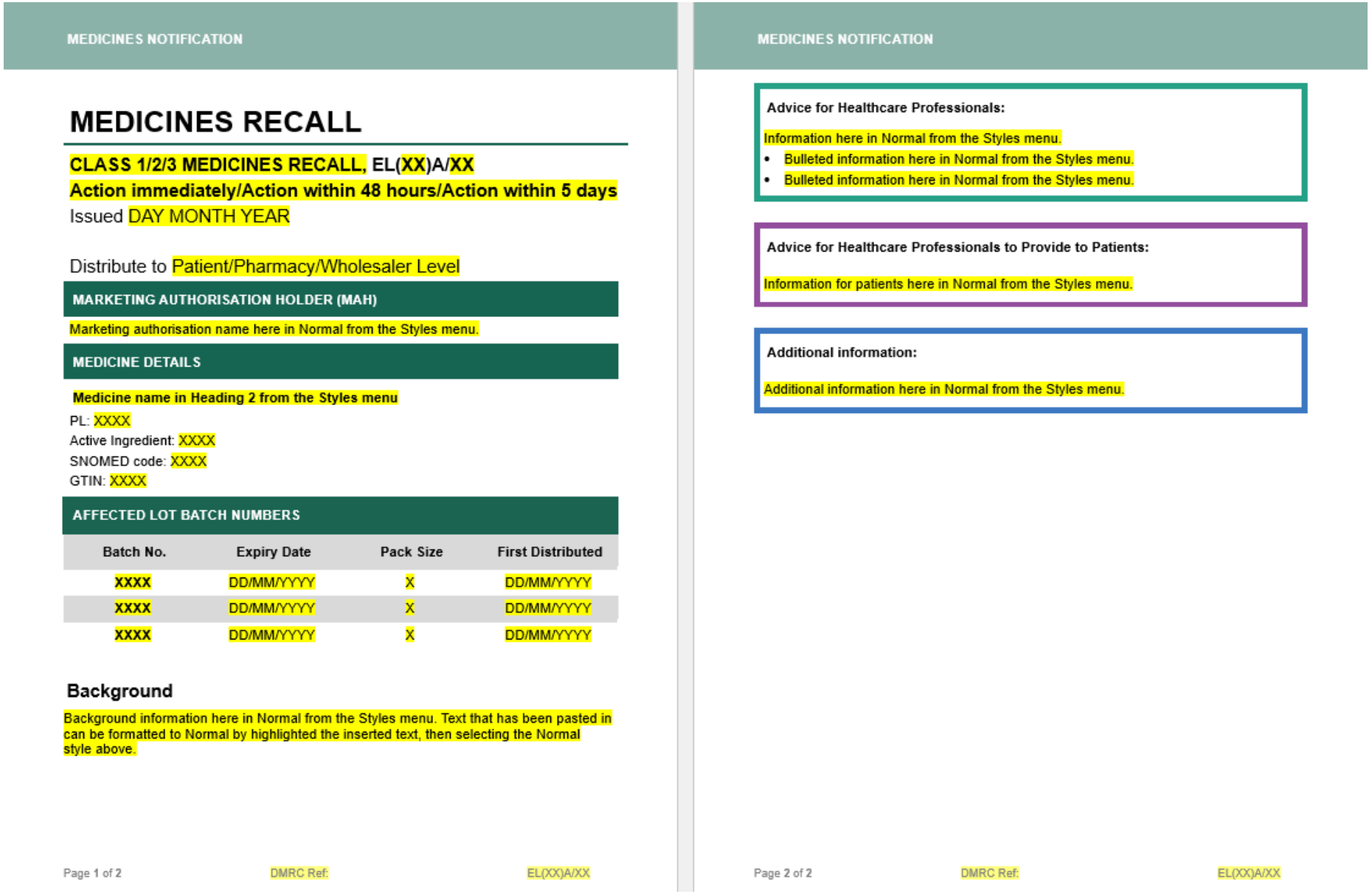
For more information about health and safety at work:

Health and Safety Executive, 151 Buckingham Palace Rd, London SW1W 9SZ

Telephone: 0300 790 6787

Or via the website https://www.hse.gov.uk

Appendix 4 - Medicines Recall Notification Examples



MEDICINES NOTIFICATION

MEDICINES RECALL

CLASS 1/2/3 MEDICINES RECALL, EL(XX)A/XX
Action immediately/Action within 48 hours/Action within 5 days
Issued DAY MONTH YEAR

Distribute to Patient/Pharmacy/Wholesaler Level

MARKETING AUTHORISATION HOLDER (MAH)

Marketing authorisation name here in Normal from the Styles menu.

MEDICINE DETAILS

Medicine name in Heading 2 from the Styles menu

PL: XXXX
Active Ingredient: XXXX
SNOMED code: XXXX
GTIN: XXXX

AFFECTED LOT BATCH NUMBERS

Batch No.	Expiry Date	Pack Size	First Distributed
XXXX	DD/MM/YYYY	X	DD/MM/YYYY
XXXX	DD/MM/YYYY	X	DD/MM/YYYY
XXXX	DD/MM/YYYY	X	DD/MM/YYYY

Background

Background information here in Normal from the Styles menu. Text that has been pasted in can be formatted to Normal by highlighted the inserted text, then selecting the Normal style above.

Page 1 of 2 DMRC Ref: EL(XX)A/XX

MEDICINES NOTIFICATION

Advice for Healthcare Professionals:

Information here in Normal from the Styles menu.

- Bulleted information here in Normal from the Styles menu.
- Bulleted information here in Normal from the Styles menu.

Advice for Healthcare Professionals to Provide to Patients:

Information for patients here in Normal from the Styles menu.

Additional information:

Additional information here in Normal from the Styles menu.

Page 2 of 2 DMRC Ref: EL(XX)A/XX

Appendix 4 - Medicines Recall Notification Examples Continued

MEDICINES NOTIFICATION

CLASS 4 MEDICINES DEFECT INFORMATION, EL(XX)A/XX

Caution In Use

Issued DAY MONTH YEAR

Distribute to Pharmacy/Wholesaler Level

MARKETING AUTHORISATION HOLDER (MAH)

Marketing authorisation name here in Normal from the Styles menu.

MEDICINE DETAILS

Medicine name in Heading 2 from the Styles menu

PL: XXXX
Active Ingredient: XXXX
SNOMED code: XXXX
GTIN: XXXX

AFFECTED LOT BATCH NUMBERS

Batch No.	Expiry Date	Pack Size	First Distributed
XXXX	DD/MM/YYYY	X	DD/MM/YYYY
XXXX	DD/MM/YYYY	X	DD/MM/YYYY
XXXX	DD/MM/YYYY	X	DD/MM/YYYY

Background

Background information here in Normal from the Styles menu. Text that has been pasted in can be formatted to Normal by highlighted the inserted text, then selecting the Normal style above.

MEDICINES NOTIFICATION

Advice for Healthcare Professionals:

Information here in Normal from the Styles menu.

- Bulleted information here in Normal from the Styles menu.
- Bulleted information here in Normal from the Styles menu.

Advice for Healthcare Professionals to Provide to Patients:

Information for patients here in Normal from the Styles menu.

Additional information:

Additional information here in Normal from the Styles menu.

Appendix 4 - Medicines Recall Notification Examples Continued

MEDICINES NOTIFICATION

MEDICINES RECALL

COMPANY LED MEDICINES RECALL, EL(XX)A/XX

Action as appropriate

Issued DAY MONTH YEAR

Distribute to Pharmacy/Wholesaler Level Recall

MARKETING AUTHORISATION HOLDER (MAH)

Marketing authorisation name here in Normal from the Styles menu.

MEDICINE DETAILS

Medicine name in Heading 2 from the Styles menu

PL: XXXX
Active Ingredient: XXXX
SNOMED code: XXXX
GTIN: XXXX

AFFECTED LOT BATCH NUMBERS

Batch No.	Expiry Date	Pack Size	First Distributed
XXXX	DD/MM/YYYY	X	DD/MM/YYYY
XXXX	DD/MM/YYYY	X	DD/MM/YYYY
XXXX	DD/MM/YYYY	X	DD/MM/YYYY

Background

Background information here in Normal from the Styles menu. Text that has been pasted in can be formatted to Normal by highlighted the inserted text, then selecting the Normal style above.

MEDICINES NOTIFICATION

Advice for Healthcare Professionals:

Information here in Normal from the Styles menu.

- Bulleted information here in Normal from the Styles menu.
- Bulleted information here in Normal from the Styles menu.

Advice for Healthcare Professionals to Provide to Patients:

Information for patients here in Normal from the Styles menu.

Additional information:

Additional information here in Normal from the Styles menu.

Appendix 5 – National Patient Safety Alert Template

National Patient Safety Alert

MHRA

TITLE

Date of Issue:			
This is a safety critical and straightforward National Patient Safety Alert. Implementation should be coordinated by a senior member of staff e.g. Head of department or equivalent roles.			

DMRC Medicines Defect Classification	NatPSA equivalent to Class 1 Recall/Class 2 Recall/Class 3 Recall/Class 4 Notification

Explanation of identified safety issue:	Actions required

For further detail, resources and supporting materials see: www.gov.uk/drug-device-alerts

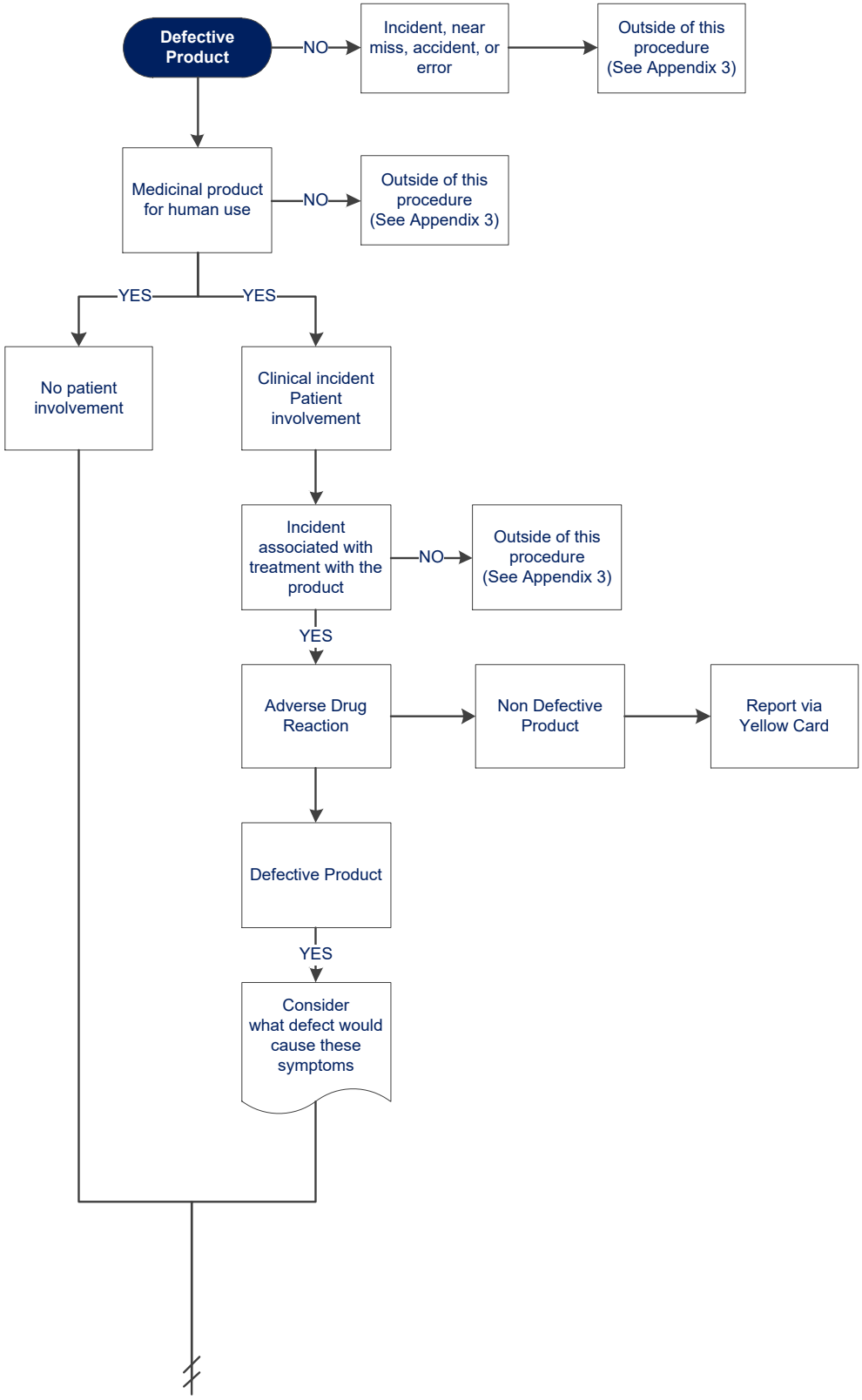
For any enquiries about this alert contact: DMRC@mhra.gov.uk 1/2

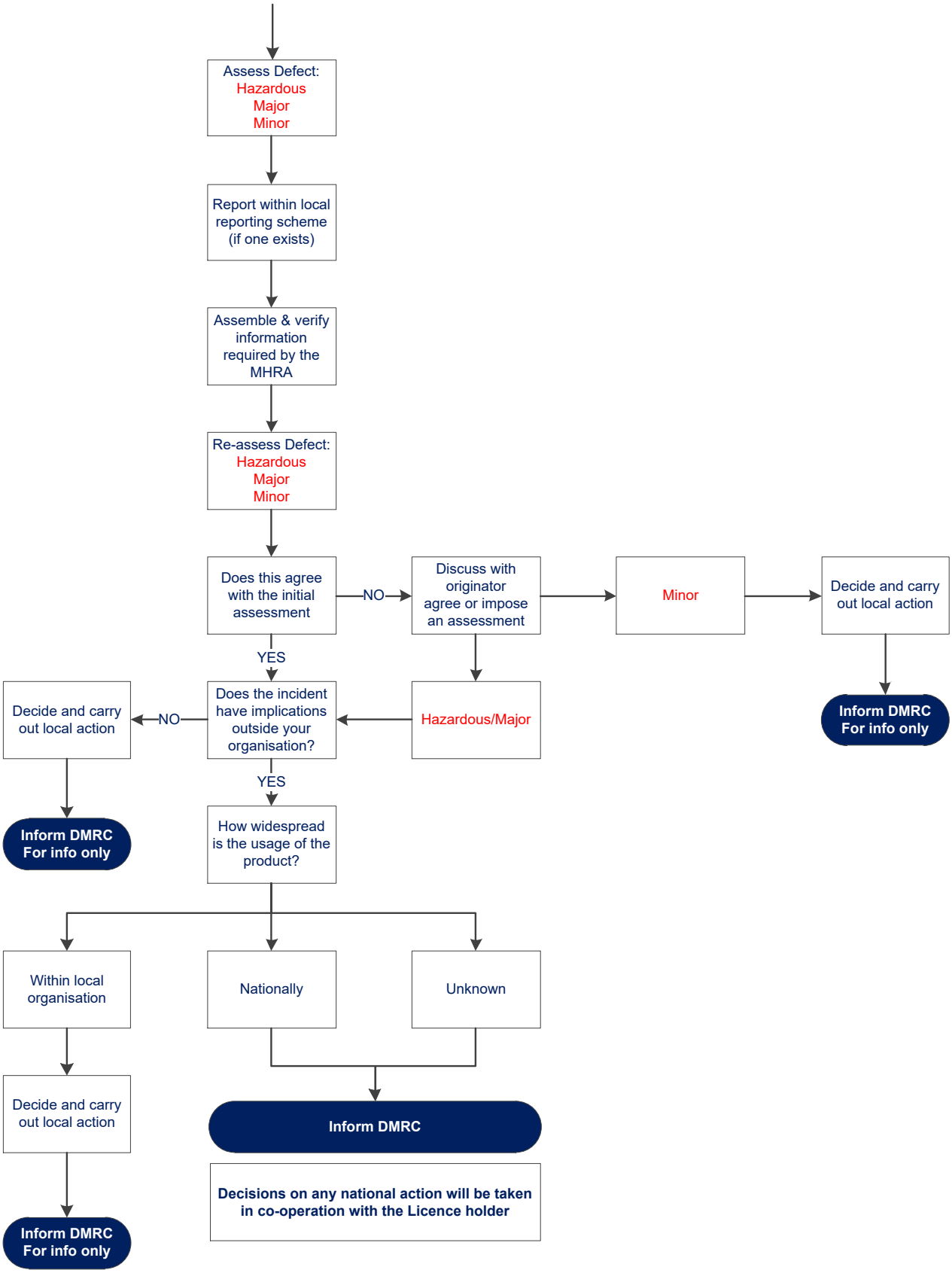
Failure to take the actions required under this National Patient Safety Alert may lead to CQC taking regulatory action

Additional information:

Please check website www.gov.uk/drug-device-alerts for when actions should be ceased or advice to check for date restriction are lifted.

Appendix 6 – Assessment Flowchart




Assess Defect:
Hazardous
Major
Minor
Report within local reporting scheme (if one exists)
Assemble & verify information required by the MHRA
Re-assess Defect:
Hazardous
Major
Minor
Does this agree with the initial assessment
NO
Discuss with originator agree or impose an assessment
Minor
Decide and carry out local action
Inform DMRC
For info only
YES
Does the incident have implications outside your organisation?
Hazardous/Major
NO
Decide and carry out local action
Inform DMRC
For info only
YES
How widespread is the usage of the product?
Within local organisation
Nationally
Unknown
Decide and carry out local action
Inform DMRC
Inform DMRC
For info only
Decisions on any national action will be taken in co-operation with the Licence holder

Appendix 7 – Defective Medicines Online Reporting Form (Licence Holders only)

Licence holders, or nominated representatives, should report defective medicine reports directly via the online reporting form, accessed via https://icsrsubmissions.mhra.gov.uk/login.

This site is already used by many organisations to submit Individual Case Safety Reports (ICSRs) and Suspected Unexpected Serious Adverse Reaction reports (SUSARs) to the MHRA. As such, your organisation may already have an organisation account for these purposes. **Before attempting to register a new account please check whether this is the case so that the correct registration process below can be followed.**

The reporting process via the portal has been designed to replicate the current process for defective medicines case reporting, removing the need to email information to the DMRC directly and provide you with access to what has been submitted. Verbal reports can be made by contacting the DMRC Helpline, and should always be made, if the report concerns a critical or major defect, or is outside of office-hours.

The data collected in the online reporting form is based on our internal processes centred around the E2B R3 Individual Case Safety Report (ICSR) Specification and Related Files, however, tailored to reporting of defective medicines.

1. **Accessing the Form for the First Time/ Registration**

As above, this portal is already used by many organisations for other purposes. All existing users will automatically be granted the ability to report using this form; it is not something that manually needs to be added to existing users' accounts.

If you are not an existing user using the portal for other purposes, you should first **determine whether your organisation is already registered, to allow you to determine the correct approach for gaining access, as below:**

i. Scenario 1: Organisation already registered on ICSR submissions portal to submit ICSRs: **not using a CRO**

There is no need for any further action from the MHRA as this can be handled internally by your organisation.

Your organisation should have existing organisation lead(s) who can set up accounts for any new users as per the standard process for new ICSR submissions portal users.

All organisation leads will be able to view both ICSR and defective medicine transmissions.

ii. Scenario 2: Organisation currently registered on ICSR submissions portal **using a CRO to submit ICSRs**

This can be handled by asking the CRO to set up users. Any CRO user(s) with the organisation lead account(s) can set up any new users for the organisation.

Please note: if an organisation lead creates a defective medicines user and your organisation has CRO users with organisation lead permissions, those CRO leads will be able to view all defective medicines reports submitted via the portal, and vice versa.

If this presents a data protection concern/ issue, please do not request that the CRO organisation lead(s) set(s) you up, but instead please email: dmrc@mhra.gov.uk explaining this; you will be able to continue to submit via email in the meantime.

iii. Scenario 3: Organisation not currently registered on ICSR submissions portal

Organisations should register by selecting **"Request company account"** on the portal login page: Sign in | MHRA. This will set up the organisation, and an organisation lead, who can subsequently create any further new users.

*Please note: if your organisation currently submits ICSRs via MHRA gateway, please enter the full company name followed by **"Defective Medicines Only"** in the Company Name field. This is to ensure that the team does not switch your route of ICSR transmissions to the portal.*

In future enhancements we will look to include "defective medicines" in the submission type drop-down.

2. Defective Medicines Reporting Form Specific Data Entry Guidance

Access to the Defective Medicines Reporting Form can be configured by selecting:

a) Report Submission

b) New Report

c) Select 'Defective Medicines Reporting Form' from the drop-down menu

d) Previously submitted reports can be access via the 'Report Management' option, with further options to export the report as a PDF or XML for use in local systems once an individual report is selected.

The guidance below provides further specific information on how to ensure that data is accurately entered into the form.

1. Organisation Case Information

Organisation Unique Identifier	UI specific to this individual case report. Must be in correct format: (Country Code)-(Company)-(text) e.g. GB-COMPANY1-2394. It may be helpful for the reporting organisation use their own reference number/digits for ease of identification.
Date of Creation	Auto-generated date, specific to the date the report was created/submitted
Date company first made aware of suspected defect	Optional date field
Date of receipt of the most recent information for this report	Optional date field
Worldwide Unique Case Identification	Auto-generated unique identifier for the case, to match the process for Yellow Card reports
Identification Number of the Report Which Is Linked to This Report	Optional field, include the MHRA reference number to which this report relates to if a previous Yellow Card report was received. i.e. in the event a Yellow Card report was received, however the issue transpired to be a quality issue, this YC report reference should be provided so the DMRC can link the case and any associated signals

2. Reporter

Source of information	Identify how this was first notified to the company, via own internal mechanism and testing or via external reporters
If ‘Customer / Patient / HCP Complaint’ selected, optional fields to complete	Provide details, where consent has been provided, to share the reporter details for any specific DMRC follow up

3. Product Information

Medicinal Product Information	Data to be provided relating to the impacted medicinal product(s). Multiple products can be added to one online reporting form by using the ‘Add’ option following completion of one suspected defective product
Product Licence Information	Free text field
Medicinal Product Name	Select via drop-down list or free text available
Active Pharmaceutical Ingredient	Free text field. Products with multiple APIs should follow the protocol below: e.g. metformin / vildagliptan
Strength (number) (Optional)	Free text field
Strength (unit) (Optional)	Select via drop-down list
Formulation (Optional)	Free text field, route of administration of the product
Product Container Type Size (Optional)	Free text field. Specific to the pack size, e.g. 28
Quantities Impacted (Optional)	Free text field. If there are multiple batches impacted, use Case Details and Further Information to capture further data
Product Licensed in the UK	Select via drop-down list
Product Legal Status	Select via drop-down list
Batch/Lot number (Optional)	Free text field. Where multiple batches are impacted, each product/batch should be added as an individual product by using the ‘Add’ option following completion of one suspected defective product

Expiry Date	Date field
Contract Manufacturing Organisation / Company Manufacturing Site Information	Free text field, specific to where the suspected defective product has been manufactured. Only company name is required here. If this is unavailable, please use name of company reporting suspected defect
Proposed Market Action(Optional)	Select via drop-down list

4. Event

Defect classification	The DMRC have proposed to utilise MedDRA (Medical Dictionary for Regulatory Activities) terminology for capturing quality defect reports. This field is a search as you type field, e.g. ‘out of specification’ will bring up a list to choose from. The DMRC assessment team will always check the correct MedDRA term has been selected. See Appendix 8 for more information.
Defect as reported by the primary source	Free text field to completion of the defect, for reports that do not originate from a complaint, a short description of the defect can be provided, however the Case Details and Further Information is preferred for a full case narrative
Defect resulted in death?	Select via drop-down list
Defect was life threatening?	Select via drop-down list
Defect caused / prolonged hospitalisation?	Select via drop-down list
Defect was disabling / incapacitating?	Select via drop-down list

Defect resulted in congenital anomaly / birth defect?	Select via drop-down list
Defect caused any other medically important condition?	Select via drop-down list

5. Case Details and Further Information

Defect description	Defect description Please provide as much information as possible, including, but not limited to, the following: (a) initial defect impact assessment and immediate action undertaken (b) health hazard evaluation/risk assessment (c) description of the root cause or ongoing hypothesis (d) proposed market action and supply impact to the UK market and other markets (e) corrective and preventative actions (CAPA) and full deviation report

6. Attachments

Attachments	Maximum individual file size 5mb. Maximum combined file size 10mb. If further files are required, please indicate this in Section 5 above and the DMRC will confirm when considering the initial assessment.

Appendix 8 – MedDRA Terms

The following MedDRA Terms provide an overview of the terms to be used for defect classification. The terms below all belong to the System Organ Class (SOC) Name: Product Issues and High Level Group Term (HLGT) Name: Product quality, supply, distribution, manufacturing and quality system issues. Industry stakeholders should select the most appropriate Preferred Term (PT) Name or Lowest Level Term (LLT) Name from the list below. Please note that this list is not exhaustive and other terms can be selected if more appropriate.

High Level Term (HLT) Name	Preferred Term (PT) Name	Lowest Level Term (LLT) Name
Product quality issues NEC	Adulterated product	Adulterated product
Manufacturing production issues	Device misassembly during manufacturing	Device misassembly during manufacturing
Product quality issues NEC	Drug delivery system issue	Drug delivery system issue
Product quality issues NEC	Drug delivery system malfunction	Drug delivery system malfunction
Product quality issues NEC	Failure of additional condition for nonprescription use	Failure of additional condition for nonprescription use
Product packaging issues	Failure of child resistant product closure	Failure of child resistant product closure
Product packaging issues	Failure of child resistant product closure	Failure of child resistant mechanism for pharmaceutical product
Quality system issues	Improper management of out of specification result	Out of specification result not investigated
Quality system issues	Improper management of out of specification result	Improper management of out of specification result
Quality system issues	Improper management of out of specification result	Out of specification result invalidated without investigation
Quality system issues	Improper management of out of specification result	Out of specification result invalidated without appropriate rationale
Manufacturing production issues	Inadequate aseptic technique in manufacturing of product	Inadequate aseptic technique in manufacturing of product
Quality system issues	Inappropriate batch production records	Missing batch production record
Quality system issues	Inappropriate batch production records	Incomplete batch production record
Quality system issues	Inappropriate batch production records	Inappropriate batch production records
Product distribution and storage issues	Inappropriate release of product for distribution	Product distribution prior to required testing
Product distribution and storage issues	Inappropriate release of product for distribution	Inappropriate release of product for distribution
Product distribution and storage issues	Inappropriate release of product for distribution	Product distribution prior to validation of process
Product distribution and storage issues	Inappropriate release of product for distribution	Product distribution prior to quality control unit release
Product quality issues NEC	Issue with additional condition for nonprescription use	Issue with additional condition for nonprescription use

Product physical issues	Liquid product physical issue	Product foaming
Product physical issues	Liquid product physical issue	Liquid phase separation
Product physical issues	Liquid product physical issue	Product appearance cloudy
Product physical issues	Liquid product physical issue	Product viscosity variable
Product physical issues	Liquid product physical issue	Liquid product flow abnormal
Product physical issues	Liquid product physical issue	Liquid product physical issue
Product physical issues	Liquid product physical issue	Liquid product consistency issue
Product physical issues	Liquid product physical issue	Abnormal liquid product viscosity
Product physical issues	Liquid product physical issue	Bubbles present in liquid product
Product physical issues	Liquid product physical issue	Increased liquid product viscosity
Product physical issues	Liquid product physical issue	Decreased liquid product viscosity
Product physical issues	Liquid product physical issue	Particle present in liquid product
Manufacturing facilities and equipment issues	Manufacturing equipment cleaning issue	Manufacturing equipment cleaning issue
Manufacturing facilities and equipment issues	Manufacturing equipment cleaning issue	Use of inappropriate cleaning agent in manufacturing
Manufacturing facilities and equipment issues	Manufacturing equipment issue	Manufacturing equipment issue
Manufacturing facilities and equipment issues	Manufacturing equipment issue	Manufacturing equipment filter issue
Manufacturing facilities and equipment issues	Manufacturing equipment issue	Manufacturing equipment high efficiency air filter issue
Manufacturing facilities and equipment issues	Manufacturing equipment sanitisation issue	Manufacturing equipment sanitization issue
Manufacturing facilities and equipment issues	Manufacturing equipment sanitisation issue	Manufacturing equipment sanitisation issue
Manufacturing facilities and equipment issues	Manufacturing equipment sterilisation issue	Manufacturing equipment sterilization issue
Manufacturing facilities and equipment issues	Manufacturing equipment sterilisation issue	Manufacturing equipment sterilisation issue
Manufacturing facilities and equipment issues	Manufacturing facilities issue	Manufacturing facilities issue
Manufacturing facilities and equipment issues	Manufacturing facilities issue	Manufacturing facility pressure differential issue
Manufacturing facilities and equipment issues	Manufacturing facilities issue	Manufacturing facility high efficiency air filter issue
Manufacturing issues NEC	Manufacturing issue	Manufacturing issue
Manufacturing laboratory controls issues	Manufacturing laboratory analytical testing issue	Manufacturing laboratory analytical testing issue

Manufacturing laboratory controls issues	Manufacturing laboratory analytical testing issue	Manufacturing laboratory analytical testing not reported
Manufacturing laboratory controls issues	Manufacturing laboratory analytical testing issue	Manufacturing laboratory analytical testing not performed due to pandemic
Manufacturing laboratory controls issues	Manufacturing laboratory analytical testing issue	Manufacturing laboratory analytical testing not documented due to pandemic
Manufacturing laboratory controls issues	Manufacturing laboratory analytical testing issue	Manufacturing laboratory analytical testing not investigated due to pandemic
Manufacturing laboratory controls issues	Manufacturing laboratory analytical testing issue	Manufacturing laboratory analytical testing issue, safety incorrectly performed
Manufacturing laboratory controls issues	Manufacturing laboratory analytical testing issue	Manufacturing laboratory analytical testing issue, purity incorrectly performed
Manufacturing laboratory controls issues	Manufacturing laboratory analytical testing issue	Manufacturing laboratory analytical testing issue, potency incorrectly performed
Manufacturing laboratory controls issues	Manufacturing laboratory analytical testing issue	Manufacturing laboratory analytical testing issue, identity incorrectly performed
Manufacturing laboratory controls issues	Manufacturing laboratory analytical testing issue	Manufacturing laboratory analytical testing issue, stability incorrectly performed
Manufacturing laboratory controls issues	Manufacturing laboratory analytical testing issue	Manufacturing laboratory analytical testing issue, sterility incorrectly performed
Manufacturing laboratory controls issues	Manufacturing laboratory analytical testing issue	Manufacturing laboratory analytical testing issue, safety not performed or documented
Manufacturing laboratory controls issues	Manufacturing laboratory analytical testing issue	Manufacturing laboratory analytical testing issue due to pandemic manpower disruption
Manufacturing laboratory controls issues	Manufacturing laboratory analytical testing issue	Manufacturing laboratory analytical testing issue, purity not performed or documented
Manufacturing laboratory controls issues	Manufacturing laboratory analytical testing issue	Manufacturing laboratory analytical testing issue, potency not performed or documented
Manufacturing laboratory controls issues	Manufacturing laboratory analytical testing issue	Manufacturing laboratory analytical testing issue, identity not performed or documented
Manufacturing laboratory controls issues	Manufacturing laboratory analytical testing issue	Manufacturing laboratory analytical testing issue, sterility not performed or documented
Manufacturing laboratory controls issues	Manufacturing laboratory analytical testing issue	Manufacturing laboratory analytical testing issue, stability not performed or documented
Manufacturing laboratory controls issues	Manufacturing laboratory analytical testing method management issue	Manufacturing laboratory analytical testing method management issue
Manufacturing laboratory controls issues	Manufacturing laboratory controls calibration issue	Manufacturing laboratory controls calibration issue
Manufacturing laboratory controls issues	Manufacturing laboratory controls issue	Manufacturing laboratory controls issue
Manufacturing laboratory controls issues	Manufacturing laboratory controls issue	Manufacturing laboratory data control issue
Manufacturing materials issues	Manufacturing material testing deviation	Manufacturing material testing deviation
Manufacturing materials issues	Manufacturing materials contamination	Manufacturing materials contamination
Manufacturing materials issues	Manufacturing materials contamination	Manufacturing excipient contamination

Manufacturing materials issues	Manufacturing materials contamination	Manufacturing raw material contamination
Manufacturing materials issues	Manufacturing materials contamination	Manufacturing inactive ingredient contamination
Manufacturing materials issues	Manufacturing materials contamination	Manufacturing active pharmaceutical ingredient contamination
Manufacturing materials issues	Manufacturing materials issue	Product raw material issue
Manufacturing materials issues	Manufacturing materials issue	Manufacturing materials issue
Manufacturing materials issues	Manufacturing materials issue	Manufacturing excipient issue
Manufacturing materials issues	Manufacturing materials issue	Manufacturing component issue
Manufacturing materials issues	Manufacturing materials issue	Manufacturing raw material issue
Manufacturing materials issues	Manufacturing materials issue	Manufacturing material impurities
Manufacturing materials issues	Manufacturing materials issue	Incoming material container defective
Manufacturing materials issues	Manufacturing materials issue	Manufacturing inactive ingredient issue
Manufacturing materials issues	Manufacturing materials issue	Lack of manufacturing materials due to pandemic
Manufacturing materials issues	Manufacturing materials issue	Shortage of inactive ingredient due to pandemic
Manufacturing materials issues	Manufacturing materials issue	Incoming material container out of specification
Manufacturing materials issues	Manufacturing materials issue	Shortage of manufacturing component due to pandemic
Manufacturing materials issues	Manufacturing materials issue	Shortage of manufacturing materials due to pandemic
Manufacturing materials issues	Manufacturing materials issue	Manufacturing active pharmaceutical ingredient issue
Manufacturing materials issues	Manufacturing materials issue	Incoming material container closure out of specification
Manufacturing materials issues	Manufacturing materials issue	Shortage of active pharmaceutical ingredient due to pandemic
Manufacturing production issues	Manufacturing process control procedure incorrectly performed	Manufacturing process control procedure incorrectly performed
Manufacturing production issues	Manufacturing process control procedure issue	Manufacturing process control procedure issue
Manufacturing production issues	Manufacturing process control procedure issue	Manufacturing process control bulk material issue
Manufacturing production issues	Manufacturing process control procedure issue	Manufacturing process control procedure filling issue
Manufacturing production issues	Manufacturing process control procedure issue	Manufacturing process control procedure media fill issue
Manufacturing production issues	Manufacturing process control procedure issue	Manufacturing process control procedure temperature issue
Manufacturing production issues	Manufacturing process control procedure issue	Manufacturing process control procedure aseptic processing issue
Manufacturing production issues	Manufacturing process control procedure issue	Manufacturing process control, process water out of specifications
Manufacturing production issues	Manufacturing process control procedure issue	Manufacturing process control procedure equipment calibration issue
Manufacturing production issues	Manufacturing process control procedure issue	Manufacturing process control procedure environmental monitoring issue
Manufacturing production issues	Manufacturing process control procedure not performed	Manufacturing process control procedure not performed

Product distribution and storage issues	Manufacturing product shipping issue	Manufacturing product shipping issue
Product distribution and storage issues	Manufacturing product storage issue	Manufacturing product storage issue
Manufacturing production issues	Manufacturing production issue	Manufacturing production issue
Manufacturing production issues	Manufacturing production issue	Manufacturing facility shutdown due to pandemic
Manufacturing production issues	Manufacturing production issue	Manufacturing production disrupted due to pandemic
Manufacturing production issues	Manufacturing production issue	Manufacturing production temporarily discontinued due to pandemic
Manufacturing production issues	Manufacturing production issue	Manufacturing production permanently discontinued due to pandemic
Manufacturing laboratory controls issues	Manufacturing stability testing issue	Manufacturing stability testing issue
Manufacturing laboratory controls issues	Manufacturing stability testing issue	Manufacturing stability testing pH issue
Manufacturing laboratory controls issues	Manufacturing stability testing issue	Stability protocol deviation not documented
Manufacturing laboratory controls issues	Manufacturing stability testing issue	Manufacturing stability testing potency issue
Manufacturing laboratory controls issues	Manufacturing stability testing issue	Manufacturing stability testing moisture issue
Manufacturing laboratory controls issues	Manufacturing stability testing issue	Manufacturing stability testing preservative issue
Manufacturing laboratory controls issues	Manufacturing stability testing issue	Manufacturing stability testing container closure issue
Manufacturing laboratory controls issues	Manufacturing stability testing issue	Manufacturing stability testing content uniformity issue
Manufacturing laboratory controls issues	Manufacturing stability testing issue	Manufacturing stability testing chemical analysis purity issue
Manufacturing materials issues	Material from non-qualified supplier used	Material from non-qualified supplier used
Manufacturing laboratory controls issues	Out of specification product testing issue	Out of specification product testing issue
Manufacturing laboratory controls issues	Out of specification product testing issue	Out of specification testing issue, not reported due to pandemic
Manufacturing laboratory controls issues	Out of specification product testing issue	Out of specification testing issue, not performed due to pandemic
Manufacturing laboratory controls issues	Out of specification product testing issue	Out of specification testing issue, not documented due to pandemic
Manufacturing laboratory controls issues	Out of specification product testing issue	Out of specification testing issue, not investigated due to pandemic
Manufacturing laboratory controls issues	Out of specification test results	Out of specification test results
Manufacturing laboratory controls issues	Out of specification test results	Out of specification test results pH

Manufacturing laboratory controls issues	Out of specification test results	Out of specification test results assay
Manufacturing laboratory controls issues	Out of specification test results	Out of specification test results density
Manufacturing laboratory controls issues	Out of specification test results	Out of specification test results potency
Manufacturing laboratory controls issues	Out of specification test results	Out of specification test results moisture
Manufacturing laboratory controls issues	Out of specification test results	Out of specification test results impurity
Manufacturing laboratory controls issues	Out of specification test results	Out of specification test results stability
Manufacturing laboratory controls issues	Out of specification test results	Out of specification test results cold flow
Manufacturing laboratory controls issues	Out of specification test results	Out of specification test results viscosity
Manufacturing laboratory controls issues	Out of specification test results	Out of specification test results friability
Manufacturing laboratory controls issues	Out of specification test results	Out of specification test results appearance
Manufacturing laboratory controls issues	Out of specification test results	Out of specification test results osmolality
Manufacturing laboratory controls issues	Out of specification test results	Out of specification test results fill volume
Manufacturing laboratory controls issues	Out of specification test results	Out of specification test results dissolution
Manufacturing laboratory controls issues	Out of specification test results	Out of specification test results shear stress
Manufacturing laboratory controls issues	Out of specification test results	Out of specification test results precipitates
Manufacturing laboratory controls issues	Out of specification test results	Out of specification test results peel adhesion
Manufacturing laboratory controls issues	Out of specification test results	Out of specification test results contamination
Manufacturing laboratory controls issues	Out of specification test results	Out of specification test results melting point
Manufacturing laboratory controls issues	Out of specification test results	Out of specification test results particle size
Manufacturing laboratory controls issues	Out of specification test results	Out of specification test results tack property
Manufacturing laboratory controls issues	Out of specification test results	Out of specification test results residual solvent
Manufacturing laboratory controls issues	Out of specification test results	Out of specification test results blend uniformity
Manufacturing laboratory controls issues	Out of specification test results	Out of specification test results specific gravity

Manufacturing laboratory controls issues	Out of specification test results	Out of specification test results container closure
Manufacturing laboratory controls issues	Out of specification test results	Out of specification test results residual monomers
Manufacturing laboratory controls issues	Out of specification test results	Out of specification test results weight uniformity
Manufacturing laboratory controls issues	Out of specification test results	Out of specification test results elemental impurity
Manufacturing laboratory controls issues	Out of specification test results	Out of specification test results disintegration time
Manufacturing laboratory controls issues	Out of specification test results	Out of specification test results preservative content
Manufacturing laboratory controls issues	Out of specification test results	Out of specification test results content of uniformity
Manufacturing laboratory controls issues	Out of specification test results	Out of specification test results delivered dose uniformity
Manufacturing laboratory controls issues	Out of specification test results	Out of specification test results for component packaged with final product
Manufacturing laboratory controls issues	Out of specification test results	Out of specification test results active pharmaceutical ingredient impurity
Manufacturing laboratory controls issues	Out of trend test result	Out of trend test result
Manufacturing laboratory controls issues	Out of trend test result	Out of trend test result assay
Manufacturing laboratory controls issues	Out of trend test result	Out of trend test result stability
Manufacturing laboratory controls issues	Out of trend test result	Out of trend test result dissolution
Product packaging issues	Packaging design issue	Packaging design issue
Product label issues	Physical product label issue	Product label loose
Product label issues	Physical product label issue	Product label missing
Product label issues	Physical product label issue	Product label damaged
Product label issues	Physical product label issue	Product label missing text
Product label issues	Physical product label issue	Physical product label issue
Product label issues	Physical product label issue	Product label placement issue
Product quality issues NEC	Product adhesion issue	Product adhesion issue
Product quality issues NEC	Product adhesion issue	Product adhesion excessive
Product quality issues NEC	Product adhesion issue	Product adhesion increased
Product quality issues NEC	Product adhesion issue	Product adhesion decreased
Product quality issues NEC	Product adhesion issue	Product adhesion insufficient

Product quality issues NEC	Product adhesion issue	Medicinal patch adhesion issue
Product quality issues NEC	Product adhesion issue	Medicinal patch adhesion increased
Product quality issues NEC	Product adhesion issue	Medicinal patch adhesion excessive
Product quality issues NEC	Product adhesion issue	Medicinal patch adhesion decreased
Product quality issues NEC	Product adhesion issue	Medicinal patch adhesion insufficient
Product physical issues	Product after taste	Product after taste
Product physical issues	Product after taste	Medication after taste
Product supply and availability issues	Product availability issue	Drug shortage
Product supply and availability issues	Product availability issue	Product availability issue
Product supply and availability issues	Product availability issue	Drug shortage due to pandemic
Product supply and availability issues	Product availability issue	Drug delivery device unavailable
Product supply and availability issues	Product availability issue	Product unavailable due to pandemic
Product label issues	Product barcode issue	Product barcode issue
Product label issues	Product barcode issue	Product barcode missing
Product label issues	Product barcode issue	Product barcode on wrong product
Product label issues	Product barcode issue	Product barcode readability issue
Product packaging issues	Product blister packaging issue	Unit-dose blister pack issue
Product packaging issues	Product blister packaging issue	Product blister packaging issue
Product packaging issues	Product blister packaging issue	Product blister packaging separated
Product physical issues	Product caught fire	Product caught fire
Product physical issues	Product caught fire	Inflammable product caught fire
Product contamination and sterility issues	Product cleaning inadequate	Product cleaning inadequate
Product packaging issues	Product closure issue	Vial stopper damage
Product packaging issues	Product closure issue	Product closure leak
Product packaging issues	Product closure issue	Product closure issue
Product packaging issues	Product closure issue	Product stopper coring
Product packaging issues	Product closure issue	Product closure missing
Product packaging issues	Product closure issue	Product closure deterioration
Product packaging issues	Product closure removal difficult	Product closure removal difficult
Product physical issues	Product coating issue	Product coating issue
Product physical issues	Product coating issue	Product coating cracked

Product physical issues	Product coating issue	Product coating incomplete
Product physical issues	Product colour issue	Product color issue
Product physical issues	Product colour issue	Product colour issue
Product physical issues	Product colour issue	Product discoloration
Product physical issues	Product colour issue	Product color leaching
Product physical issues	Product colour issue	Product discolouration
Product physical issues	Product colour issue	Product colour leaching
Product physical issues	Product colour issue	Product color variation
Product physical issues	Product colour issue	Product colour variation
Product packaging issues	Product commingling	Product commingling
Product packaging issues	Product commingling	Wrong product and correct product in same container
Product packaging issues	Product commingling	Wrong and correct product strengths in same container
Product quality issues NEC	Product complaint	Product complaint
Product quality issues NEC	Product complaint	Pharmaceutical product complaint
Product quality issues NEC	Product compounding quality issue	Product compounding quality issue
Product packaging issues	Product container issue	Product vial breakage
Product packaging issues	Product container issue	Product container leak
Product packaging issues	Product container issue	Product container issue
Product packaging issues	Product container issue	Product container damaged
Product packaging issues	Product container issue	Product container discoloration
Product packaging issues	Product container issue	Product container type incorrect
Product packaging issues	Product container issue	Product container discolouration
Product packaging issues	Product container issue	Product container size incorrect
Product packaging issues	Product container seal issue	Product container seal issue
Product contamination and sterility issues	Product contamination	Product contamination
Product contamination and sterility issues	Product contamination	Device contamination during use
Product contamination and sterility issues	Product contamination	Preservation media contamination
Product contamination and sterility issues	Product contamination	Device contamination prior to use
Product contamination and sterility issues	Product contamination	Therapeutic product contamination

Product contamination and sterility issues	Product contamination	Pharmaceutical product contamination
Product contamination and sterility issues	Product contamination chemical	Product contamination chemical
Product contamination and sterility issues	Product contamination microbial	Device colonisation
Product contamination and sterility issues	Product contamination microbial	Device colonization
Product contamination and sterility issues	Product contamination microbial	Product biofilm coating
Product contamination and sterility issues	Product contamination microbial	Product contamination mold
Product contamination and sterility issues	Product contamination microbial	Product contamination mould
Product contamination and sterility issues	Product contamination microbial	Product contamination viral
Product contamination and sterility issues	Product contamination microbial	Product contamination fungal
Product contamination and sterility issues	Product contamination microbial	Product contamination exotoxin
Product contamination and sterility issues	Product contamination microbial	Product contamination bacterial
Product contamination and sterility issues	Product contamination microbial	Product contamination microbial
Product contamination and sterility issues	Product contamination microbial	Product contamination endotoxin
Product contamination and sterility issues	Product contamination microbial	Product contamination endospores
Product contamination and sterility issues	Product contamination physical	Product contamination soil
Product contamination and sterility issues	Product contamination physical	Product contamination hair
Product contamination and sterility issues	Product contamination physical	Product contamination metal
Product contamination and sterility issues	Product contamination physical	Product contamination glass
Product contamination and sterility issues	Product contamination physical	Product contamination insect
Product contamination and sterility issues	Product contamination physical	Product contamination plastic
Product contamination and sterility issues	Product contamination physical	Product contamination physical
Product contamination and sterility issues	Product contamination physical	Product contamination plant matter
Product contamination and sterility issues	Product contamination physical	Product contamination animal matter

Product contamination and sterility issues	Product contamination physical	Product contamination inorganic matter
Product contamination and sterility issues	Product contamination physical	Product contamination foreign material
Product contamination and sterility issues	Product contamination physical	Product contamination particulate matter
Product contamination and sterility issues	Product contamination with body fluid	Product contamination with blood
Product contamination and sterility issues	Product contamination with body fluid	Product contamination with body fluid
Product contamination and sterility issues	Product contamination with body fluid	Product contamination with blood derivative
Counterfeit, falsified and substandard products	Product counterfeit	Spurious product
Counterfeit, falsified and substandard products	Product counterfeit	Falsified product
Counterfeit, falsified and substandard products	Product counterfeit	Product counterfeit
Counterfeit, falsified and substandard products	Product counterfeit	Pharmaceutical product counterfeit
Product quality issues NEC	Product delivery mechanism issue	Product dropper issue
Product quality issues NEC	Product delivery mechanism issue	Product dropper missing
Product quality issues NEC	Product delivery mechanism issue	Product dropper tip issue
Product quality issues NEC	Product delivery mechanism issue	Product dosing cup missing
Product quality issues NEC	Product delivery mechanism issue	Product dropper tip missing
Product quality issues NEC	Product delivery mechanism issue	Product spray mechanism issue
Product quality issues NEC	Product delivery mechanism issue	Product delivery mechanism issue
Product quality issues NEC	Product delivery mechanism issue	Product dropper improperly calibrated
Product quality issues NEC	Product delivery mechanism issue	Product dropper calibration unreadable
Product quality issues NEC	Product delivery mechanism issue	Product dosing cup markings unreadable
Product physical issues	Product deposit	Product deposit
Product physical issues	Product deposit	Product crystals present
Product physical issues	Product deposit	Product precipitate present
Product physical issues	Product deposit	Product sedimentation present
Product physical issues	Product deposit	Ophthalmic medication precipitation
Product packaging issues	Product desiccant issue	Product desiccant issue
Product packaging issues	Product desiccant issue	Product desiccant damaged
Product packaging issues	Product desiccant issue	Product desiccant missing

Product quality issues NEC	Product design issue	Product design issue
Product distribution and storage issues	Product distribution issue	Product shipment delay
Product distribution and storage issues	Product distribution issue	Product distribution issue
Product distribution and storage issues	Product distribution issue	Product shipment delay due to pandemic
Product distribution and storage issues	Product distribution issue	Product distribution delay due to pandemic
Product physical issues	Product dosage form issue	Product dosage form issue
Product physical issues	Product dosage form issue	Product dosage form imprint incorrect
Product physical issues	Product dosage form issue	Product dosage form identification issue
Product label issues	Product expiration date issue	Product expiration date issue
Product label issues	Product expiration date issue	Product expiration date missing
Product label issues	Product expiration date issue	Product expiration date incorrect
Product label issues	Product expiration date issue	Product expiration date illegible
Product label issues	Product expiration date issue	Product label expiration date extended
Product quality issues NEC	Product formulation issue	Product ingredient issue
Product quality issues NEC	Product formulation issue	Product formulation issue
Product quality issues NEC	Product formulation issue	Wrong active ingredient in product
Product physical issues	Product gel formation	Product gel formation
Product label issues	Product identification number issue	Product identification number issue
Product label issues	Product identification number issue	Product identification number missing
Product label issues	Product identification number issue	Product identification number incorrect
Product label issues	Product identification number issue	Product identification number illegible
Product quality issues NEC	Product impurity	Product impurity
Product quality issues NEC	Product impurity	Product impurities found
Counterfeit, falsified and substandard products	Product label counterfeit	Product label counterfeit
Product label issues	Product label issue	Misbranded product
Product label issues	Product label issue	Carton label issue
Product label issues	Product label issue	Product label issue
Product label issues	Product label issue	Carton label missing
Product label issues	Product label issue	Product leaflet issue

Product label issues	Product label issue	Product leaflet missing
Product label issues	Product label issue	Product leaflet text wrong
Product label issues	Product label issue	Product package insert issue
Product label issues	Product label issue	Product label text illegible
Product label issues	Product label issue	Product package insert missing
Product label issues	Product label issue	Product label strength missing
Product label issues	Product label issue	Product package insert incorrect
Product label issues	Product label issue	Product label strength incorrect
Product label issues	Product label issue	Product package insert text wrong
Product label issues	Product label on wrong product	Wrong product leaflet
Product label issues	Product label on wrong product	Product label on wrong product
Product physical issues	Product leakage	Product leakage
Product label issues	Product lot number issue	Product lot number issue
Product label issues	Product lot number issue	Product lot number missing
Product label issues	Product lot number issue	Product charge number issue
Product label issues	Product lot number issue	Product lot number incorrect
Product label issues	Product lot number issue	Product lot number illegible
Product quality issues NEC	Product measured potency issue	Product measured subpotent
Product quality issues NEC	Product measured potency issue	Product measured superpotent
Product quality issues NEC	Product measured potency issue	Product measured potency issue
Product quality issues NEC	Product measured potency issue	Product measured potency decrease over time
Product physical issues	Product odour abnormal	Product odor abnormal
Product physical issues	Product odour abnormal	Product odour abnormal
Product physical issues	Product odour abnormal	Product smell abnormal
Product quality issues NEC	Product origin unknown	Product origin unknown
Product quality issues NEC	Product origin unknown	Product manufacturer unknown
Product packaging issues	Product outer packaging issue	Product outer packaging issue
Counterfeit, falsified and substandard products	Product packaging counterfeit	Product packaging counterfeit
Product packaging issues	Product packaging difficult to open	Product packaging difficult to open
Product packaging issues	Product packaging issue	Bag port defect
Product packaging issues	Product packaging issue	Product packaging issue

Product packaging issues	Product packaging quantity issue	Package empty units
Product packaging issues	Product packaging quantity issue	Package volume overfill
Product packaging issues	Product packaging quantity issue	Package volume underfill
Product packaging issues	Product packaging quantity issue	Package quantity incorrect
Product packaging issues	Product packaging quantity issue	Package dosage units missing
Product packaging issues	Product packaging quantity issue	Product packaging quantity issue
Product packaging issues	Product packaging quantity issue	Unit-dose blister packaging partial fill
Product physical issues	Product physical consistency issue	Product physical consistency issue
Product physical issues	Product physical issue	Tablet issue
Product physical issues	Product physical issue	Capsule open
Product physical issues	Product physical issue	Product burst
Product physical issues	Product physical issue	Capsule issue
Product physical issues	Product physical issue	Tablet cracked
Product physical issues	Product physical issue	Tablet damaged
Product physical issues	Product physical issue	Tablet chipped
Product physical issues	Product physical issue	Product friable
Product physical issues	Product physical issue	Tablet clumping
Product physical issues	Product physical issue	Cracked product
Product physical issues	Product physical issue	Product damaged
Product physical issues	Product physical issue	Product clumping
Product physical issues	Product physical issue	Product crumbling
Product physical issues	Product physical issue	Product explosion
Product physical issues	Product physical issue	Capsule separation
Product physical issues	Product physical issue	Product overheating
Product physical issues	Product physical issue	Capsule extra shell
Product physical issues	Product physical issue	Capsule fill abnormal
Product physical issues	Product physical issue	Tablet physical issue
Product physical issues	Product physical issue	Capsule physical issue
Product physical issues	Product physical issue	Product physical issue
Product physical issues	Product physical issue	Soft gelatin capsule burst
Product physical issues	Product physical issue	Scored tablet splitting issue

Product physical issues	Product physical issue	Tablet does not break into pre-defined pieces
Product packaging issues	Product primary packaging issue	Product primary packaging issue
Product packaging issues	Product primary packaging issue	Medicinal product interaction with primary packaging
Manufacturing production issues	Product process control issue	Product process control issue
Manufacturing production issues	Product quality control issue	Product quality control issue
Product quality issues NEC	Product quality issue	Product quality issue
Product quality issues NEC	Product quality issue	Product quality complaint
Product quality issues NEC	Product quality issue	Product lot specific issue
Product quality issues NEC	Product quality issue	Topical product difficult to remove from application site
Product physical issues	Product reconstitution quality issue	Product reconstitution quality issue
Product physical issues	Product shape issue	Product shape issue
Product physical issues	Product size issue	Product size issue
Product physical issues	Product solubility abnormal	Product solubility abnormal
Product physical issues	Product solubility abnormal	Product solubility increased
Product physical issues	Product solubility abnormal	Product solubility decreased
Product physical issues	Product solubility abnormal	Product dissolution abnormal
Product physical issues	Product solubility abnormal	Product dissolution decreased
Product physical issues	Product solubility abnormal	Product dissolution increased
Product contamination and sterility issues	Product sterility issue	Device sterility issue
Product contamination and sterility issues	Product sterility issue	Product sterility issue
Product contamination and sterility issues	Product sterility issue	Product sterility lacking
Product contamination and sterility issues	Product sterility issue	Product sterile packaging missing
Product contamination and sterility issues	Product sterility issue	Product sterile packaging disrupted
Product quality issues NEC	Product substitution issue	Product substitution issue
Product quality issues NEC	Product substitution issue	Biosimilar product substitution issue
Product quality issues NEC	Product substitution issue	Product substitution issue brand to brand
Product quality issues NEC	Product substitution issue	Product substitution issue brand to generic
Product quality issues NEC	Product substitution issue	Product substitution issue generic to brand
Product quality issues NEC	Product substitution issue	Product substitution issue generic to generic

Product quality issues NEC	Product substitution issue	Product substitution issue reference biologic product to biosimilar
Product supply and availability issues	Product supply issue	Supply shortage
Product supply and availability issues	Product supply issue	Product supply issue
Product supply and availability issues	Product supply issue	Product delay due to pandemic
Product supply and availability issues	Product supply issue	Drug supply chain interruption
Product supply and availability issues	Product supply issue	Drug supply chain interruption due to pandemic
Product supply and availability issues	Product supply issue	Drug import channel interruption due to pandemic
Product supply and availability issues	Product supply issue	Product supply chain interruption due to pandemic
Product quality issues NEC	Product tampering	Product tampering
Product quality issues NEC	Product tampering	Medication tampering
Product quality issues NEC	Product tampering	Tampering with medication
Product physical issues	Product taste abnormal	Product taste abnormal
Product physical issues	Product taste abnormal	Peculiar taste of pharmaceutical product
Product distribution and storage issues	Product temperature excursion issue	Product temperature excursion issue
Product supply and availability issues	Recalled product	Recalled product
Counterfeit, falsified and substandard products	Suspected counterfeit product	Suspected falsified product
Counterfeit, falsified and substandard products	Suspected counterfeit product	Suspected counterfeit product
Product contamination and sterility issues	Suspected product contamination	Suspected product contamination
Product quality issues NEC	Suspected product quality issue	Suspected product quality issue
Product quality issues NEC	Suspected product tampering	Suspected product tampering

Appendix 9 – References

Howard Abbott. Managing Product Recall. 1991. Pitman, London.

Batch recall of pharmaceutical products. 1994. Association of the British Pharmaceutical Industry, London.

Council Directive 2003/94/EC laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products

EudraLex - Volume 4 Good manufacturing practice (GMP) Guidelines

EU Guidelines on Good Distribution Practice of medicinal products for human use (2013/C 343/01)

The Human Medicines Regulations 2012 [SI 2012/1916]

A more detailed listing of relevant legislation can be found in the Rules and Guidance for Pharmaceutical Manufacturers and Distributors 2014

Medicines, Ethics and Practice (MEP). - https://www.rpharms.com/publications/the-mep